REMARKS

I. Disposition of the Claims

Claims 1-5 and 63-68 are pending. Claims 1- 5 stand rejected. Claims 63-68 are new and should be allowable.

Claims 1 and 3 have been amended. Support for each amendment to claim 1 is in the specification as-filed. Support for the amendment to claim 3 is in the specification as-filed (e.g., p. 10, ll. 6-10; pp. 28-30).

Claims 67-68 should be grouped according to the restriction requirement of record and should be allowable when claim 1 is allowable. Claims having a product/use-of-the-same-product relationship are allowable when the product is allowable. MPEP § 821.04. For example, if a composition comprising A is allowable, then the use of the same composition should be allowable. In this case, claim 1 recites a compound and claims 67-68 recite the same base compound's use. Thus, there should be no serious burden to examine the method of claims 67-68 once claim 1 is allowable.

Similarly, claims 63-64 should be grouped accordingly and should be allowable when claim 3 is allowable.

Claims 65-66 should be grouped accordingly and should be allowable when claim 1 is allowable.

II. Written Description Rejection

Claim 1 is rejected for lacking a written description of provisos 7-9. Office action, pp. 3-4. The present version of the claims avoids this issue. Thus, the rejection should be withdrawn.

III. Enablement Rejection

Claims are assumed enabled. MPEP § 2164.04. Indeed, when challenging a specification's enablement, the PTO must not only explain why it doubts a claim's presumptively enabling disclosure but also cite supporting evidence for its assertion. Id.

Claim 5, nevertheless, has been rejected without citing supporting evidence. Office action, pp. 4-5. Indeed, the thrust of the PTO's argument is that undue experimentation would have been required since one of ordinary skill in the art would have had "to speculate" what the "active truncated derivatives thereof" were. Id. This finding, however, is contradicted by the evidence of record, and thus the rejection is improper and should be withdrawn.

Specifically, the term "active truncated derivatives thereof" is part of a larger phrase, namely, "insulin growth factor and 'active truncated derivatives thereof.'" For example, insulin growth factor and active truncated derivatives thereof are characterized by U.S. Pat. No. 5,780,484 as follows: "Numerous neurotrophic factors have been identified in the art and any of those factors may be utilized in the compositions of this invention. These neurotrophic factors include, but are not limited to, nerve growth factor (NGF), insulin growth factor (IGF-1) and its active truncated derivatives such as gIGF-1...." The '484 patent, col. 6, ll. 20-25 (emphasis added) (enclosed for consideration).

This quoted disclosure itself is evidence that IGF's "active truncated derivatives," such as gIGF-1, were not speculative as of the '484 patent's filing date, November, 1996. In other words, since this time, ascertaining the meaning of "active truncated derivatives thereof" was within, not outside, the level of ordinary skill in the art.

And there is more evidence contradicting the PTO's position. The '484 patent's claim 8 reads:

> 8. The method according to claim 7, wherein said neurotrophic factor is selected from nerve growth factor (NGF), insulin growth factor (IGF) and active truncated derivatives thereof, acidic fibroblast growth factor (aFGF), basic fibroblast growth factor (bFGF), platelet-derived growth factors (PDGF), brain-derived neurotrophic factor (BDNF), ciliary neurotropic factors CNTF), glial cell-derived neurotropic factor (GDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5).

Id. (emphasis added), see also claim 13. This claim recites using "insulin growth factor (IGF) and active truncated derivatives thereof." This claim is presumed enabled, as all U.S. patent's claims are. Thus, ascertaining the meaning of "active truncated derivatives thereof" at the time the '484 patent was filed required no speculation, as the meaning was within the level of ordinary skill in the art.

Not only is the '484 patent evidence that contradicts the PTO's position, but at least six other U.S. Patents also contradict it. U.S. Pat. No. 5,840,736, col. 6, ll. 31-33, claims 8, 25 (enclosed for consideration); U.S. Pat. No. 5,935,954, col. 19, ll. 1-2, claims 12, 15 (enclosed for consideration); U.S. Pat. No. 6,124,328, col. 8, ll. 64-65, claim 9 (enclosed for consideration); U.S. Pat. No. 6,172,086, col. 6, ll. 36-37, claims 9, 14 (enclosed for consideration); U.S. Pat. No. 6,284,778, col. 6, ll. 37-38, claim 6 (enclosed for consideration); U.S. Pat. No. 6,326,387, col. 8, ll. 54-55, claim 19 (enclosed for consideration). For sure, this evidence of record provides only one reasonable conclusion: ascertaining the meaning of "active truncated derivatives thereof" was within the level of ordinary skill in the art one of ordinary skill in the art when the present specification was filed.

And when this evidence (the seven patents above) is weighed against the PTO's evidence (none), there is only one conclusion: the evidence and explanation show claim 5 is enabled by the present specification. Thus, the rejection is improper and should be withdrawn.

IV. Indefiniteness Rejections

Claims 1 and 5 have been rejected as indefinite. Office action, pp. 6-8. The present version of claim 1 avoids this issue. Claim 1's rejection should be withdrawn. Claim 5's rejection is improper and should be withdrawn.

The PTO urges that the term "active truncated derivatives thereof" is indefinite and effectively created a requirement for defining this term in the specification as-filed. Id., pp. 7-8 ("The specification should disclose every aspect of Applicant's invention. The specification fails to define the expression... Applicant has failed to specify ... where in the instant specification the expression ... is defined."). This requirement is neither required by law nor required by regulation, as there is absolutely no requirement for the specification to define all of a claim's terms. MPEP § 2173.02.

Definite claims "reasonably apprise" one of ordinary skill in the art of their scope. Id. Relevant to whether a term "reasonably apprises" one of ordinary skill in the art is the meaning that artisan would have given to the term at the time of the invention. Id.

In this rejection, the PTO has never disputed that the term "active truncated derivatives thereof" would have reasonably apprised one of ordinary skill in the art of its scope. It could not. The seven patents cited above and enclosed for consideration use the term in their claims, which are presumptively definite. In other words, the evidence of record indicates that the term "active truncated derivatives thereof" would have reasonably apprised one of ordinary skill in the art of its scope. Thus, the rejection is improper and should be withdrawn.

V. Anticipation Rejections

There are four anticipation rejections, each addressed under a separate heading. Under an additional heading, the novelty of new claims is discussed.

A. GB 1,503,244

Claim 3 has been rejected as anticipated by example 1(A) of GB 1,503,244. Office action, p. 9. A claim may be anticipated by a reference only if that reference describes it. MPEP § 2131. GB 1,503,244 describes a compound of Example 8 but never describes a "pharmaceutically acceptable carrier" and thus never anticipates any composition comprising a "pharmaceutically acceptable carrier."

Specifically, even if GB 1,503,244 may add it compounds to a carrier to form compositions (p. 17, ll. 32-38), there is no reason to believe that GB 1,503,244's carriers would be "pharmaceutically acceptable." Carriers are not necessarily "pharmaceutically acceptable." Indeed, GB 1,503,244's carriers may even contain insecticide, nematocide, fertilizer, synergetic agents, another herbicide, or fungicide or plant growth regulators. GB 1,503,244, p. 17, ll. 36-38. As such, GB 1,503,244 seems totally unconcerned with "pharmaceutically acceptable" protocol.

The PTO, nevertheless, cannot ignore any claim limitations, including "pharmaceutically acceptable carrier," which GB 1,503,244 never describes. Thus, GB 1,503,244 never anticipates the composition of claim 3, and the rejection should be withdrawn.

B. Jamieson (U.S. Pat. No. 4,230,709)

Claim 3 stands rejected as anticipated by Example 8 of Jamieson. Office action, p. 9. Jamieson never describes a compound of claim 3 and thus never anticipates claim 3.

Specifically, Jamieson describes 2-**n-butyl**-tetrahydro-1H-pyrrolo[1,2-c]imidazole-1,3-(2H)-dione. Jamieson, col. 5, Ex. 8. Focus on the n-butyl group, which cannot be made by the D and R of the compound of claim 3, especially since R can no longer be a hydrogen atom. As Jamieson never describes a compound of claim 3, Jamieson, therefore, never anticipates the composition of claim 3, and the rejection should be withdrawn.

C. WO 96/06846 (Lopez-Rodriguez)

Claims 3-5 stand rejected as anticipated by compound 1g of WO 96/06846. Office action, p. 9. WO 96/06846 (translation), however, describes arylpiperazines, which contain a piperazine unit.

A piperazinyl group contains two nitrogen atoms. On the other hand, claim 3 reads, in relevant part under R's definition, "wherein when R is an alicyclic monocyclic heterocyclic ring containing a nitrogen heteroatom, the alicyclic monocyclic heterocyclic ring contains only one nitrogen heteroatom." As a result, R differs from a piperazinyl group. Moreover, claims 4-5 depend from 3. Thus, WO 96/06846 (translation) neither describes nor anticipates claims 3-5, and the rejection should be withdrawn.

D. Lopez-Rodriguez (J. Med. Chem (1997) 30:1648-56)

Claim 3 has been rejected as anticipated by compound 1a of Lopez-Rodriguez. Office action, p. 9, Lopez-Rodriguez describes arylpiperazines, which contain a piperazine unit containing two nitrogen atoms. On the other hand, for the reasons just noted, claim 3's R differs from a piperazinyl group. Thus, Lopez-Rodriguez neither describes nor anticipates claim 3, and the rejection should be withdrawn.

E. Claims 63-68 are new.

New claim 63 is new over each reference GB 1,503,244; Jamieson; WO 96/06846; and Lopez-Rodriguez. Claim 63 recites a pharmaceutical composition comprising a compound having the limitations of the compound of claim 1, a compound not rejected of record.

New claim 64 is new over each reference GB 1,503,244; Jamieson; WO 96/06846; and Lopez-Rodriguez. Claim 64 recites a pharmaceutical composition comprising a compound having the limitations of the compound of claim 2, a compound not rejected of record.

New claims 65-66 are new over each reference GB 1,503,244; Jamieson; WO 96/06846; and Lopez-Rodriguez. Claim 65 recites a pharmaceutical composition excluding the compounds cited of record. See provisos.

New claims 67-68 are allowable at least for the same reasons that claim 1 is allowable.

VI. Obviousness Rejections

Claims 1-5 stand rejected as allegedly prima facie obvious over the teachings of Wakabayashi (JP 52-083686), GB 1,503,244, Jamieson, and WO 96/06846, each taken alone or in combination with each other when similar utilities are asserted. Office action, pp. 11-14. This rejection is improper and should be withdrawn.

A prima facie case cannot be established unless the prior art provides motivation, i.e., a desirable reason, for making the claimed invention. MPEP § 2143.01. Nor can it be established unless the prior art provides a reasonable expectation of success. MPEP § 2143.02. Yet a prima facie case has not been established here for the evidence and explanation lack of the required motivation and expectation of success.

According to the PTO, the required motivation is that "indiscriminate selection of 'some' among 'many' is prima facie obvious." Office action, p. 13. This quote is based on dictum from In re Lemin, 141 USPQ 814 (CCPA 1964) (enclosed for consideration), and special attention should be given to the term "indiscriminate." In Lemin, the prior art's generic disclosure totally embraced the claimed compound. Lemin, 141 USPQ 815. Thus, "indiscriminately" selecting any claimed compound would have produced a prior art compound.

This case, however, vastly differs from Lemin, where the claimed compound was totally embraced by the prior art's generic disclosure. Here, "indiscriminately" selecting an embodiment of the claimed invention would not necessarily produce any compound from the generic disclosures of Wakabayashi, GB 1,503,244, Jamieson, or WO 96/06846. Clearly, the compounds of these generic disclosures most definitely may differ from those of the claimed invention. And indiscriminate selection of a species of the claimed invention produces at best a mere chance of reaching an embodiment from these generic disclosures. Of course, random chance differs from the required motivation to reach the claimed invention. MPEP § 2144.08.

For sure, under all circumstances, "it is essential that Office personnel find some motivation or suggestion to make the claimed invention" in order to establish a prima facie case. MPEP § 2144.08 II A. Since the record and explanation lack the required motivation, the rejection is improper and should be withdrawn.

Nor does the explanation and evidence of record contain the required reasonable expectation of success. According to the PTO, the teachings of Wakabayashi, GB 1,503,244, Jamieson, and WO 96/06846 provide a basis for predicting activity of compounds to treat central nervous system disorders. Office action, p. 13. Yet Wakabayashi concerns germicides (p. 1); GB 1,503,244 concerns compound for fungicidal and herbicidal activity (p. 1); Jamieson concerns compound for treating asthma (col. 1); and WO 96/06846 concerns 5-HT_{1A} ligands (p. 2 translation). How these references can

provide a reasonable expectation of success of making compounds to treat central nervous system disorders is not in the evidence or explanation of record. Since the evidence or explanation of record lack the required reasonable expectation of success, the rejection is improper and therefore should be withdrawn.

Finally, the combination of teachings is improper. Combining references requires the desirability of the combination. MPEP § 2143.01. As just noted, the teachings of Wakabayashi, GB 1,503,244, Jamieson, and WO 96/06846 are disparate. There is no reason of record to combine them. Thus, the rejection over the combination is improper and should be withdrawn.

CONCLUSION

Applicant respectfully requests reconsideration and reexamination of the present application in view of the foregoing amendments and in view of the above reasons.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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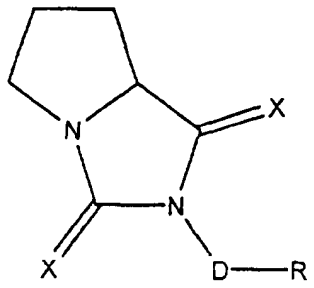
Enclosures:

In re Lemin, 141 USPQ 814 (CCPA 1964);
U.S. Pat. No. 5,780,484;
U.S. Pat. No. 5,840,736;
U.S. Pat. No. 5,935,954;
U.S. Pat. No. 6,124,328;
U.S. Pat. No. 6,172,086;
U.S. Pat. No. 6,284,778; and
U.S. Pat. No. 6,326,387.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

1. (Twice Amended) A compound of the formula:



or a pharmaceutically acceptable salt, ester or solvate wherein:

each X independently is O, S, or NR_2;

R_2 is selected from the group consisting of cyano, nitro, hydrogen, C_1-C_4 alkyl, hydroxy, and C_1-C_4 alkoxy;

D is a direct bond or C_1-C_8 alkyl or alkenyl;

R is selected from the group consisting of hydrogen, phenyl, biphenyl, cyclopropyl, [cylobutyl,] cyclobutyl, cyclopentyl, cycloheptyl, cyclooctyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, isoindolyl, indolinyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, tetrahydrofuranyl, tetrahydropyranyl, pyridyl, pyrrolyl, pyrrolidinyl, pyridinyl, pyrimidinyl, purinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinolizinyl, furyl, benzofuranyl, thiophenyl, imidazolyl, oxazolyl, benzoxazolyl, benzoxazinyl, thiazolyl, isoxazolyl, isotriazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, trithianyl, indolizinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, benzopyranyl,

thienyl, tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, phenazinyl, phenothiazinyl, phenoxazinyl, and adamantyl;

wherein R may be optionally substituted with one substituent which is selected from the group consisting of halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;

wherein when R is hydrogen, then D is C_5-C_7 alkyl or C_5-C_8 alkenyl;

wherein when R is phenyl and D is a bond, then R is substituted with phenyl, hydroxyl, trifluoromethyl, C_2-C_6 straight or branched chain alkyl or alkenyl, C_3-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, or benzyloxy;

wherein when R is 4-trifluoromethylphenyl, then both X substituents are O;

wherein when both X substituents are O and D is C_2 alkyl, then R is not phenyl substituted with 4-nitro or 4-amino;

wherein when both X substituents are O and R is H, D is not C_1-C_8 alkyl;

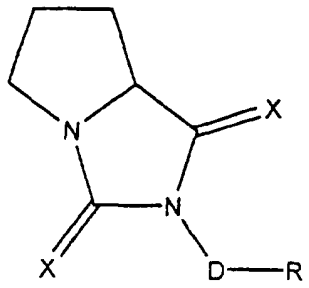
wherein when both X substituents are O and D is C_1 alkyl, R is not phenyl;

wherein when both X substituents are O and D is a direct bond, then R is not phenyl substituted with 3-trifluoromethyl; [4-methoxy, 4-fluoro, 4-chloro, 3,5-dichloro, 4-methyl, 4-ethoxy, 4-bromo or 3,4-dichloro;]

wherein when one X is O, the other X is S, and D is a direct bond, then R is not phenyl substituted with 3-trifluoromethyl; [4-methoxy, 4-bromo, 3,4-dichloro, 4-methyl, 4-chloro, 4-nitro or 3,5-dichloro;] and

wherein when both X substituents are O and D is C_3 straight chain alkyl, then R is not phenyl substituted with 3-methoxy.

3. (Amended) A pharmaceutical composition comprising an effective amount of a compound and a pharmaceutically acceptable carrier, wherein the compound is of the formula:



where

each X independently is O, S, or NR_2;

R_2 is selected from the group consisting of cyano, nitro, hydrogen, C_1-C_4 alkyl, hydroxy, and C_1-C_4 alkoxy;

D is a direct bond or C_1-C_8 alkyl or alkenyl;

R is [hydrogen, or] an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, **wherein when R is an alicyclic monocyclic heterocyclic ring containing a nitrogen heteroatom, the alicyclic monocyclic heterocyclic ring contains only one nitrogen heteroatom**;

wherein R is optionally substituted with one substituent selected from the group consisting of hydrogen, halo, hydroxyl, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenyl, phenoxy, benzyloxy, and amino;

or a pharmaceutically acceptable salt, ester, or solvate thereof.